IBD on the AMU

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Newcastle upon Tyne Hospitals NHS Foundation Trust
A talk in 3 parts...

- Recognising & managing acute, severe UC (ASUC)
- Complications of IBD treatment that may present to AIM
- Immune checkpoint inhibitor colitis
  - Coming to an AMU near you.
Acute Severe UC

Recognition, management and pitfalls
Recognising ASUC

• Not **acute** in onset
• Family history
• Age & vascular risk factors
• Travel
• Dodgy takeaways
• Immunosuppressed?
• Drugs (NSAIDs, biologics)

**Differential diagnoses**
- Infectious
- Ischaemic
- Drug induced
- Diverticulitis
What does ‘severe’ mean?

- Truelove and Witts criteria (1950s)

| Table 1.2. Disease activity in UC [adapted from Truelove & Witts32]. |
|---------------------------------|------------------|------------------|------------------|
| Mild | Moderate ‘in between mild and severe’ | Severe |
| Bloody stools/day | < 4 | 4 or more if | ≥ 6 and |
| Pulse | < 90 bpm | ≤ 90 bpm | > 90 bpm or |
| Temperature | < 37.5°C | ≤ 37.8°C | > 37.8°C or |
| Haemoglobin | > 11.5 g/dl | ≥ 10.5 g/dl | < 10.5 g/dl or |
| ESR | < 20 mm/h | ≤ 30 mm/h | > 30 mm/h or |
| CRP | Normal | ≤ 30 mg/l | > 30 mg/l |
Predicting outcome in severe ulcerative colitis

S P L Travis, J M Farrant, C Ricketts, D J Nolan, N M Mortensen, M G W Kettlewell, D P Jewell

Background—Simple criteria are needed to predict which patients with severe ulcerative colitis will respond poorly to intensive medical treatment and require colectomy.

Aims—To find out if the early pattern of change in inflammatory markers or other variables could predict the need for surgery and to evaluate the outcome of medical treatment during one year follow up.

Treatment with intravenous corticosteroids and a policy of early colectomy originally reduced the mortality in severe episodes of ulcerative colitis from 31–61% in the 1950s\(^1\) to 5–9% in 1962.\(^2\)\(^3\) Although mortality outside specialist centres in 1974 remained alarmingly high (37%, \(^4\)), in specialist or district hospitals with an interest in colitis it is now 3% or less, including operative mortality.\(^5\)\(^–\)\(^7\) These

Still 2.9%
Old school, not (in this case) the best school.
Investigations

• CT (in the era of low dose scanners)
• Stool
  • C diff
  • C&S
• Stool chart (patient completed)
• Flexi sig (within 24-48 hours)
Real world case - LB

- 36 yrs, teacher
- Diagnosed with pan UC 6 months prior
- Previous breast cancer (5yrs)
  - Resection, chemoradioth, still on tamoxifen
- On mesalazine and recently started prednisolone for flare
- Has also had a single dose of infliximab as OP
Admission with ASUC D1

- Diarrhoea
  - 12x in 24 hours
- Haematochazia
- Abdominal pain
- Fever

- Pulse 120 bpm
- BP 128/75 mm/Hg
- Temp 37.8 degrees

- Hb 70 g/l
- WCC 13000
- CRP 25
- Alb 25
Treatment

• Wait for results of stool cultures or crack on?

• Steroids
  • What dose?

• LMWH
  • Even if rectal bleeding?

• Antibiotics?

IV HYDROCORTISONE 100mg QDS

ABSOLUTELY (&TEDS)

ONLY IF INFECTION THOUGHT LIKELY
D2

• Flexi sig:

D3

• Histology pending
• CRP now 11
• B/O x8
• Feels better
Day 3

• If B/0 > 8 times and/or CRP > 45
  • Risk of colectomy 85% without rescue therapy¹

• **Therefore** – if after 3 days of IV steroids, stool freq still high, then good idea to start discussing alternative treatments

• Specialist IBD team should be involved by now

¹ ECCO guidelines 2016
D4

- Still frequent diarrhoea
  - B/O x8

- CRP up 26, Alb fallen 22

- CT - pancolitis

- Surgeons contacted, stoma nurses see
D5

• Still no improvement
• Histology
  • Severe UC, no CMV, nil to suggest Crohn’s

• Previous none response to infliximab
• Patient not keen on ciclosporin
• Opt for surgery
D7 to 1 year

• Subtotal colectomy, end ileostomy

• Post op bilateral ileofemoral DVTs
• Despite LMWH & TEDS
  • (Tamoxifen is prothrombotic)

• IPAA 1 yr later = remains well and happy
Pitfalls in the mx of ASUC

1. Acute severe UC mimics
   • Enteric pathogens
   • Ischaemia
   • CMV

2. VTE
   • Emma Stuart Memorial symposium

3. Masked perforation with steroids

4. Waiting too long before giving rescue therapy
   • No longer than D+5
Acute complications
OF IMMUNOSUPPRESSION IN IBD
Modern management of IBD:

1) More aggressive immunosuppression

2) Earlier in disease course (young patients)
If admission diagnosis is ‘Crohn’s flare’, **THINK** – is it actually a complication of treatment?

### What are the main side-effects of 6MP/Azathioprine?

<table>
<thead>
<tr>
<th>Event</th>
<th>Estimated Frequency (annual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop therapy due to adverse event</td>
<td>11% (11/100)</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>2% (2/100)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2% (2/100)</td>
</tr>
<tr>
<td>Hepatitis/abnormal liver tests</td>
<td>2% (2/100)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>3% (3/100)</td>
</tr>
<tr>
<td>Serious Infections</td>
<td>5% (5/100)</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>0.04% (4/10,000)</td>
</tr>
</tbody>
</table>

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### What are the main side-effects associated with anti-TNF therapy?

<table>
<thead>
<tr>
<th>Event</th>
<th>Estimated Frequency (annual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop therapy due to adverse event</td>
<td>10% (10/100)</td>
</tr>
<tr>
<td>Infusion or injection site reactions</td>
<td>3%-20%</td>
</tr>
<tr>
<td>Drug related lupus-like reaction</td>
<td>1% (1/100)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>3% (3/100)</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>0.06% (6/10,000)</td>
</tr>
<tr>
<td>Multiple sclerosis, heart failure, serious liver injury</td>
<td>Case reports only</td>
</tr>
</tbody>
</table>

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Maintenance

Good safety data from disease registries

• Sepsis and infections (double risk of serious infection)

• Reactivation of latent TB (0.2/100 person yrs)

• No increased risk of solid organ cancer

• Increased risk of non-melanoma skin cancer

antiTNF

ASUC

<table>
<thead>
<tr>
<th>Serious adverse reactions by clinical system</th>
<th>n=135</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>8</td>
</tr>
<tr>
<td><em>Clostridium difficile</em></td>
<td>1</td>
</tr>
<tr>
<td>Chest infection</td>
<td>3</td>
</tr>
<tr>
<td>Skin infection</td>
<td>0</td>
</tr>
<tr>
<td>Post-surgical</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
<tr>
<td>Neurological</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1</td>
</tr>
<tr>
<td>Renal</td>
<td>0</td>
</tr>
<tr>
<td>Malignancy*</td>
<td>1</td>
</tr>
<tr>
<td>Allergy or infusion reaction</td>
<td>2</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory</td>
<td>1</td>
</tr>
<tr>
<td>Hepatic</td>
<td>0</td>
</tr>
</tbody>
</table>

CONSTRUCT study, Lancet Gastro Hep, 2016
• Thiopurine use is associated with lymphoma
  • ~5 fold risk versus no thiopurine use
  • But still rare (<1 per 1000 patient years)
• EBV driven, PTLD like
  • EBV reactivation

• 2x fatal cases of haemophagocytic lymphohistiocytosis (HLH)
  • Primary EBV infection

Haemophagocytic Lymphohistiocytosis (HLH):
• Fever
• Splenomegaly
• Pancytopenia
• Hyperferritinemia (>10,000)
• Haemophagocytosis
• Hypertryglyceridaemia
Exposure to thiopurines and lymphomas in IBD

Beaugerie L et al., Lancet 2009;374:1617-25
Risk of Developing non-Hodgkin's Lymphoma

Patient receiving anti-TNF + Immunomodulator Therapy for 1 year

~190,000 patients (median age 43 yrs)

Median f/u 6.7 years

Risk of lymphoma
- Thiopurine aHR 2.6
- AntiTNF aHR 2.41
- Combo aHR 6.11
Summary – acute treatment complications

• We use lots more immunosuppression and in combination
• Infection, both classical and opportunistic are biggest risks
• May present to AMU with a complication of tx rather than the disease itself
• Increase risk of lymphoma, particularly >50 years
Immune checkpoint inhibitor colitis

COMING TO AN AMU NEAR YOU
Real world case - SB

• 62 year old male, previously fit and well
• Expat, living in Spain
  Metastatic adenocarcinoma lung
  Advanced, stage IV at presentation

• Jan’ 16 - March’17: partial response to Cisplatin & Pemetrexed

April 2017: Nivolumab (ICPi)
After Cycle 5 (Spain)

• Watery loose stool
• Crampy abdominal pain
• generally unwell
• Started 40mg prednisolone
• Flies home

AMU @ RVI

• Bloody diarrhoea 20x
• Weight loss
• SBP 90 mmHg, p 105
• Hb 127
• CRP 48
• Alb 32
• Cr 223
Immune checkpoint inhibitors

Median overall survival is now *years* in advanced melanoma with combination ipi+nivo

<table>
<thead>
<tr>
<th></th>
<th>NIVO+IPI (n=313)</th>
<th>NIVO (n=313)</th>
<th>IPI (n=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3-4</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Skin AEs, %</td>
<td>60.4</td>
<td>5.8</td>
<td>43.8</td>
</tr>
<tr>
<td>Rash</td>
<td>28.4</td>
<td>2.9</td>
<td>22.7</td>
</tr>
<tr>
<td>Pruritus</td>
<td>35.1</td>
<td>1.9</td>
<td>20.4</td>
</tr>
<tr>
<td><strong>Gastrointestinal AEs, %</strong></td>
<td>47.6</td>
<td>15.3</td>
<td>21.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45.4</td>
<td>9.6</td>
<td>20.8</td>
</tr>
<tr>
<td>Colitis</td>
<td>11.5</td>
<td>8.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Endocrine AEs, %</td>
<td>32.3</td>
<td>9.8</td>
<td>15.7</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>16.0</td>
<td>0.3</td>
<td>9.3</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>10.2</td>
<td>1.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Hepatic AEs, %</td>
<td>31.6</td>
<td>15.8</td>
<td>7.3</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>17.9</td>
<td>8.6</td>
<td>3.8</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>15.7</td>
<td>6.1</td>
<td>4.2</td>
</tr>
<tr>
<td>Pulmonary AEs, %</td>
<td>7.3</td>
<td>1.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>6.7</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Renal AEs, %</td>
<td>6.4</td>
<td>1.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Elevated creatinine</td>
<td>4.2</td>
<td>0.3</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Checkmate 067, Wolchok ASCO 2016, Wolchok NEJM 2017
### New International Indications since 2017

<table>
<thead>
<tr>
<th>Solid malignancies</th>
<th>Haematological malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pembrolizumab (Merck &amp; Co.)</td>
</tr>
<tr>
<td>Breast</td>
<td>[ ]</td>
</tr>
<tr>
<td>CRC</td>
<td>[ ]</td>
</tr>
<tr>
<td>Prostate</td>
<td>[ ]</td>
</tr>
<tr>
<td>NSCLC</td>
<td>[ ]</td>
</tr>
<tr>
<td>Bladder</td>
<td>[ ]</td>
</tr>
<tr>
<td>Cervical</td>
<td>[ ]</td>
</tr>
<tr>
<td>HbN</td>
<td>[ ]</td>
</tr>
<tr>
<td>SCLC</td>
<td>[ ]</td>
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<tr>
<td>Pancreatic</td>
<td>[ ]</td>
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<tr>
<td>Gastric</td>
<td>[ ]</td>
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<tr>
<td>Ovarian</td>
<td>[ ]</td>
</tr>
<tr>
<td>RCC</td>
<td>[ ]</td>
</tr>
<tr>
<td>Oesophageal</td>
<td>[ ]</td>
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<tr>
<td>Mesothelioma</td>
<td>[ ]</td>
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<tr>
<td>Melanoma</td>
<td>[ ]</td>
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<tr>
<td>HCC</td>
<td>[ ]</td>
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<tr>
<td>STS</td>
<td>[ ]</td>
</tr>
<tr>
<td>Brain</td>
<td>[ ]</td>
</tr>
<tr>
<td>Thyroid</td>
<td>[ ]</td>
</tr>
<tr>
<td>Merkel cell</td>
<td>[ ]</td>
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<tr>
<td>NHL</td>
<td>[ ]</td>
</tr>
<tr>
<td>MM</td>
<td>[ ]</td>
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<tr>
<td>MDS</td>
<td>[ ]</td>
</tr>
<tr>
<td>CML</td>
<td>[ ]</td>
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<tr>
<td>CLL</td>
<td>[ ]</td>
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<tr>
<td>AML</td>
<td>[ ]</td>
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<tr>
<td>HL</td>
<td>[ ]</td>
</tr>
<tr>
<td>ALL</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

- Early development (phase I)
- Mid-late development (phase I/II, phase II, phase II/III or phase III)
- Marketed product
- Academic (IST) or industry collaborations
Case 2

• Treated with high dose steroid
  
  **70mg IV methylprednisolone (1mg/kg)**

• No response
• Rescue therapy with infliximab
  • Colitis resolved

• Nivolumab stopped
  • But there is data to demonstrate good, durable responses in patients who develop irAE
ESMO Clinical Practice Guidelines

MILD
G1 Supportive Fluids Loperamide
G2 CONTINUE ICPI (<3 days)

MODERATE
G1 Oral Prednisolone (>14 days) 0.5-1mg/kg
G2 ICPI WITHELD (>3 days)

SEVERE
G3 IV Methylprednisolone
G4 ICPI WITHELD (1-2mg/kg)

RESCUE THERAPY
IV INFliximab (5mg/kg)

• Adapted from: Haanen Annal Oncol 2017
ICPi colitis summary

- ICPi therapy has revolutionised cancer therapy
- Colitis is a common complication of ICPi therapy
- It is especially common in anti-PD1/antiCTLA-4 combination therapy
- Colitis is reversible and steroid responsive in many patients
- Rescue therapy with infliximab is effective
Microbiome, diet and disease?

Doctors say that you should eat 5 pieces of fruit or veg a day to remain healthy. Last week I ate 5 mouldy plums and that night I shat the bed. What’s healthy about that?

Mark J Barnsley